The HIV-AIDS Debate Is Over

By Stephen J. O'Brien, Ph.D.

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Epidemiologists have documented the presence of the human immunodeficiency virus (or antibodies to HIV) in more than 95% of the world's AIDS patients (1-6). Scientists who have examined the clinical data collected from AIDS patients are convinced that it is HIV, and no other etiologic agent, which causes the gradual decline in CD4 cell counts that leads to severe immunosuppression and AIDS. Why, then, is there any lingering doubt about the cause of AIDS? Why, in spite of overwhelming evidence to the contrary, do a small number of scientists -- and a larger number of infected individuals -- continue to insist that HIV does not cause AIDS?

A decade ago, when a highly regarded molecular virologist named Peter Duesberg first suggested that AIDS was caused not by HIV but by a combination of recreational drugs, hyperstimulation of the immune system, and possibly even antiretroviral drugs themselves (7), the scientific community felt obliged to respond to Duesberg's hypothesis. The fact that his argument was largely rhetorical, and was unsupported by the preponderance of the data then available, made Duesberg's claim dubious, but it did not altogether rule out his theory. Erring on the side of excessive caution, respected members of the scientific community gave Duesberg's hypothesis more serious consideration than the data alone seemed to merit -- and they rejected his theory as untenable (1, 4, 8-10).

On the face of it, Duesberg's counter-theory made little sense. If AIDS was caused by recreational drugs like nitrate inhalants, also known as "poppers," and prescription drugs like zidovudine, also known as AZT, then how could one account for the millions of cases of AIDS that had occurred in Third World countries, where these drugs were not available? And how did one explain AIDS in hemophiliacs, transfusion recipients, and infants born to HIV-infected mothers -- none of whom had used poppers or AZT?

Duesberg's answer was, frankly, bizarre. He simply announced that these AIDS patients -- the vast preponderance of those infected worldwide -- did not actually have AIDS. They had something, of course -- and they were dying of it. But it wasn't AIDS, Duesberg insisted. The fact that these patients tested positive for the presence of HIV or antibodies to HIV, that they had declining CD4 cell counts, and that they developed the opportunistic infections that are regarded as AIDS-defining illnesses did not seem to trouble Duesberg, whose principal research had been with cancer-causing retroviruses in chickens.

Duesberg's assault on the epidemiology and clinical pathology of AIDS -- an assault mounted by someone who had little experience in either discipline -- blindsided workers in the field. Initially, at least, they were disconcerted by the volume and volubility of

Duesberg's attacks on their data, and they were temporarily disarmed by this scientist who disdained reasonable scientific argument and scientific proof.

With each passing year the evidence that HIV causes AIDS grew more persuasive and less refutable, even at the purely rhetorical level. But even as this evidence mounted, Duesberg and his minions grew increasingly shrill and hectoring (11-15). Their unsupported but high-decibel jeremiads garnered some media attention -- in 1993, for instance, the *London Times* labeled the epidemic "a tragic myth" -- and even respectable scientific journals felt obliged to address the issue again and again (8-10, 16-18), simply because Duesberg and his outspoken supporters raised the issue again and again.

In a singularly sensational and reckless response to this furor, a 65-year-old Florida clinician actually inserted a syringe into the finger of an AIDS patient and then injected himself with the same syringe -- to emphasize his conviction that HIV infection does not cause AIDS (19). In the same vein, Duesberg himself once proposed to let Robert Gallo inoculate him with HIV. That Duesberg never went through with this publicity-generating ploy leads one to wonder if he has reservations about his own theory.

The HIV-AIDS debate grew more acrimonious, and more futile, with each exchange, and it eventually became apparent that no amount of scientific evidence, no matter how unimpeachable, would silence the naysayers. Indeed, the decade-long controversy culminated last year with the publication of Duesberg's 772-page polemic, *Inventing the AIDS Virus*, a farrago of rhetorical hubris, unsupported speculation, and selective critiques of the tens of thousands of papers written by scientists who are persuaded that HIV is the etiologic agent in AIDS.

In the end, Duesberg's alternative explanation for the AIDS epidemic was little more than an indictment of a certain kind of gay lifestyle, one that is popularly perceived as consecrated to casual sex and equally casual drug-taking (16). As such, his hypothesis was but a variant of the mean-spirited fundamentalist belief that people with AIDS are victims of their own vices.

Over the past decade Duesberg's counter-theory has found two natural audiences, neither with rigorous scientific training. First, he has found an evergreen audience among certain voracious investigative journalists of the lay press. Controversy and conspiracy theories sell better than sobersided factual analysis, especially in fringe publications, and Duesberg has provided those publications with more than his share of both. But even redoubtable journals like *Science* and *Nature* have repeatedly featured Duesberg's arguments, generally under the rubric of point-counterpoint (8-11, 16, 17, 20-22). The controversy surrounding Duesberg's claims has doubtless been perceived as good copy by the publishers and the readers of all of these publications.

Duesberg's second, and far larger, audience is men and women who know (or strongly suspect) that they are infected with HIV. There is a certain irony in this, of course, since these adherents to Duesberg's counter-theory are implicitly joining in his

condemnation of their life-style choices. But there is also pathos in this situation. Antibody-positive individuals have been given a near-certain death sentence . . . *if* HIV causes AIDS. But if something else -- poppers, prescription drugs, African swine fever virus -- causes AIDS, and if that causative agent can be identified, then maybe, just maybe, their prognosis is less grim.

Denial is a device for coping with death-dealing illnesses, and it is hardly limited to patients with HIV infection -- as any clinician who has ever treated a chronic smoker can attest to. The dilemma here is that the form of denial that is manifested by the HIV-infected individuals who espouse Duesberg's views thwarts our best efforts to prevent the spread of HIV and treat those who are infected.

How HIV fulfills Koch's postulates

The mainstay of Duesberg's counter-theory is that HIV cannot be the etiologic agent in AIDS because it does not satisfy Koch's famous postulates -- postulates that must be fulfilled before it can be concluded that a particular bacterial agent causes a particular disease. Robert Koch, the discoverer of the anthrax bacillus, first posited his three postulates in the late nineteenth century (23), and although minor modifications have been suggested over the years -- chiefly to accommodate technological advances (24, 25) -- the basic tenets remain essentially unchanged. For more than a century Koch's postulates have served as the litmus test for determining the cause of any epidemic disease:

- Epidemiological association: the suspected cause must be strongly associated with the disease
- Isolation: the suspected pathogen can be isolated -- and propagated -- outside the host
- Transmission pathogenesis: transfer of the suspected pathogen to an uninfected host, man or animal, produces the disease in that host.

During the early years of the AIDS epidemic, both defenders and critics of the theory that HIV causes AIDS agreed that HIV failed to completely fulfill Koch's postulates (1, 7, 13, 14, 25). As defenders of the theory were quick to point out, a number of other diseases, notably typhoid fever, diphtheria, and leprosy, also fail to meet these stringent tests of causality -- yet there is no controversy about what causes these illnesses. We know the pathogens that produce these diseases; what we cannot do with consistency is culture those pathogens *in vitro.*

This was the problem with HIV as well, until recently. There was little question, even among the counter-theorists, that HIV clearly satisfied the first and second of Koch's postulates, but it proved considerably harder to show that HIV also fulfilled the third. Today, however, overwhelming epidemiological and experimental data have been

assembled to fulfill all three of Koch's postulates, establishing to a virtual certainty that HIV causes AIDS (26).

Demonstrating the epidemiological concordance of HIV exposure and AIDS was relatively straightforward, once the etiologic agent had been identified. Numerous studies have shown, for example, that prompt and progressive depletion of CD4 lymphocytes -- and a subsequent diagnosis of AIDS -- follows HIV seroconversion in the vast majority of HIV-infected hemophiliacs (27, 28), and HIV antibodies have been detected in more than 90% of transfusion recipients who received blood from donors who were HIV-positive. In the latter group seroconversion has likewise led to progressive depletion of CD4 cells and the onset of AIDS (27-29).

Two recent cohort studies of HIV-positive hemophiliacs have provided an even more direct link between HIV infection and mortality: They show a ten-fold increase in deaths among antibody-positive patients compared to uninfected individuals, irrespective of the severity of the subjects' hemophilia (30, 31). Significantly, since the screening of donated blood for the presence of HIV was instituted, new infections have dropped almost to zero among hemophiliacs and transfusion recipients -- further proof that HIV is the cause of AIDS.

The fact that HIV itself (or antibodies to the virus) can be detected in more than 95% -- but fewer than 100% -- of AIDS patients worldwide is explained by the relative insensitivity of the early tests for the presence of HIV in patients' peripheral blood. By the more sensitive HIV RNA assays now used to detect the virus, it is possible to confirm the presence of HIV in individuals who have as few as 20 viral particles per mL of blood (*see* "The HIV RNA Assay: A Valuable New Diagnostic Tool," Vol. 2, No. 2).

Sensitive as these new diagnostic tests are, they will not detect HIV in all profoundly immunocompromised patients -- not because the virus fails Koch's test for pathogenicity but because other disorders cause the body's immune system to collapse (32, 33). Certain drugs also produce immune suppression, as do chemical carcinogens, irradiation, and cigarette smoke.

The isolation component of Koch's postulates has been repeatedly demonstrated since the discovery of HIV. Scores of isolates have been cultured from AIDS patients; the virus has been cultivated in fresh human T lymphocytes; and cultured-cell lines have been developed for *in vitro* propagation (10, 34). This leaves only Koch's third postulate -- transmission pathogenesis -- as a matter of contention. Ethical considerations preclude the experimental inoculation of uninfected individuals with HIV, and this makes empirical verification of Koch's last postulate exceedingly difficult.

Difficult, but not impossible. For while we cannot deliberately infect anyone with HIV merely to satisfy Koch's postulates and Duesberg's curiosity, we can examine the evidence that has been gathered on healthcare workers who were accidentally infected with HIV in the course of their professional work. Take, for example, the cases of three laboratory technicians who were inadvertently exposed to the HTLV-IIIb strain of HIV-1

while working with that strain in their laboratories (35). All three of these technicians developed antibodies to HIV, and within five years all three showed marked CD4 lymphocyte depletion. Two had their CD4 counts fall to less than 200 cells/mm3, and one of those developed PCP.

In all three of these cases it was possible to establish the precise phylogenetic type of the virus that had infected the laboratory workers. When genetic sequencing tests were performed on the laboratory virus and on viral samples taken from the three workers, the sequence divergence was less than 3% (36). This low level of divergence is equivalent to the variation observed in cases of HIV transmission from mothers to their infants -- and it is less than one third as great as the extent of variation seen when viral samples from unconnected patients are compared (37, 38). Thus, these three unfortunate individuals provide *prima facie* evidence of transmission pathogenesis, Koch's third postulate.

This same high level of genetic concordance was also seen when the C.D.C. compared viral samples taken from a Florida dentist who died of AIDS with samples taken from five of his patients who tested positive for HIV and who had no HIV risk factors other than multiple visits to the dentist for invasive procedures (39, 40). Two independent research groups reached the same conclusion after examining the HIV gene sequences of these six individuals: the dentist had almost certainly infected his patients in the course of those invasive procedures, although the experts could not say exactly how those infections had occurred (41-44).

It is unlikely that we will ever learn how transmission occurred in this unique cluster of infections, but the genetic data gathered from the victims of this tragedy teach us an important lesson: They establish, as conclusively as science can establish such things, that when HIV is inadvertently transferred from a person with AIDS to an uninfected host, it does indeed produce AIDS in that host (45). And thus it satisfies the last, and most rigorous, of Koch's postulates.

Pathogenesis has also been demonstrated in various animal models. HIV-2, a less virulent strain of HIV largely restricted to West Africa, causes CD4 depletion and AIDS-like pathology in yellow baboons (46), and at least 12 strains of simian immunodeficiency virus, a close cousin of HIV, induce CD4 depletion and cause AIDS-defining illness in Asian macaques (47-51). Given that Koch's third postulate can be fulfilled by transmission to either man or animal, these examples offer strong supplemental evidence that HIV causes AIDS.

Conclusion

The last year has seen dramatic breakthroughs in the treatment of HIV infection, and these advances reinforce the causal role of HIV in AIDS. Triple-drug combination

therapy has resulted in dramatic reductions in viral burden, sometimes to undetectably low levels, and these reductions are generally accompanied by increases in CD4 cell counts.

The discovery that certain chemokines are crucial secondary receptors for HIV infection (52) led to the discovery, in my laboratory and others, of a deletion mutation in the CKR5 gene that confers protection against HIV infection (53). In homozygous individuals this mutation prevents infection, and in heterozygous individuals it delays disease progression by several years (*see* "Genetic mutation appears to confer immunity to HIV," Vol. 2, No. 5). If HIV were not the cause of AIDS, the new antiretroviral "cocktails" would not work and CKR5, a key receptor for HIV infection, would not delay the onset of AIDS.

It is time to recognize that the HIV-AIDS debate is over, as an academic exercise and as a practical matter. This decade-long debate may have been constructive at first, because it obliged scientists to give careful consideration to the epidemiological and clinical data they were gathering, but it has become a dangerous diversion. The doubt that it has fostered, particularly among our patients, carries the potential for great harm: it can lead those at high risk of infection to ignore prevention messages, and it can keep those who are infected from benefiting from recent advances in therapy. The debate should cease, and all energies should be directed toward developing an effective vaccine against HIV and curative treatments for those who are infected.

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